

## THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of modulating sphingosine kinase functional activity, said method comprising contacting said sphingosine kinase with an effective amount of an agent for a time and under conditions sufficient to modulate phosphorylation of said sphingosine kinase wherein inducing or otherwise agonising said phosphorylation up-regulates said sphingosine kinase activity and inhibiting or otherwise antagonising said phosphorylation down-regulates sphingosine kinase activity.
2. A method of modulating cellular activity, said method comprising contacting said cell with an effective amount of an agent for a time and under conditions sufficient to modulate the phosphorylation of sphingosine kinase wherein inducing or otherwise agonising said phosphorylation up-regulates said cellular activity and inhibiting or otherwise antagonising said phosphorylation down-regulates said cellular activity.
3. The method according to claim 1 or 2 wherein said sphingosine kinase is human sphingosine kinase.
4. The method according to any one of claims 1-3 wherein said phosphorylation is modulated at S<sup>225</sup>.
5. The method according to claim 4 wherein said agent binds, links or otherwise associates with S<sup>225</sup>.
6. The method according to any one of claims 1-5 wherein modulation of said phosphorylation is modulation of proline-directed protein kinase catalysed phosphorylation.
7. The method according to claim 6 wherein said proline directed kinase is ERK1, ERK2 or CDK2.

- 60 -

8. The method according to claim 7 wherein said proline directed kinase is ERK2.
9. The method according to any one of claims 1-8 wherein said modulation is down-regulation.
10. The method according to claim 9 wherein said agent is U0126.
11. The method according to claim 9 wherein said agent is PD98059.
12. A method for the treatment and/or prophylaxis of a condition in a mammal, which condition is characterised by aberrant, unwanted or otherwise inappropriate cellular activity, said method comprising administering to said mammal an effective amount of an agent for a time and under conditions sufficient to modulate phosphorylation of sphingosine kinase wherein inducing or otherwise agonising said phosphorylation up-regulates said cellular activity and inhibiting or otherwise antagonising said phosphorylation down-regulates said cellular activity.
13. A method for the treatment and/or prophylaxis of a condition in a mammal, which condition is characterised by aberrant, unwanted or otherwise inappropriate sphingosine kinase functional activity, said method comprising administering to said mammal an effective amount of an agent for a time and under conditions sufficient to modulate phosphorylation of sphingosine kinase wherein inducing or otherwise agonising said phosphorylation up-regulates said sphingosine kinase functional activity and inhibiting or otherwise antagonising said phosphorylation down-regulates said sphingosine kinase functional activity.
14. The method according to claim 12 or 13 wherein said sphingosine kinase is human sphingosine kinase.
15. The method according to any one of claims 12-14 wherein said phosphorylation is modulated at S<sup>225</sup>.

- 61 -

16. The method according to claim 15 wherein said agent binds, links or otherwise associates with S<sup>225</sup>.
17. The method according to any one of claims 12-16 wherein modulation of said phosphorylation is modulation of proline-directed protein kinase catalysed phosphorylation.
18. The method according to claim 17 wherein said proline directed kinase is ERK1, ERK2 or CDK2.
19. The method according to claim 18 wherein said proline directed kinase is ERK2.
20. The method according to any one of claims 12-19 wherein said modulation is down-regulation.
21. The method according to claim 20 wherein said cellular activity is induced by TNF.
22. The method according to claim 21 wherein said condition is a neoplastic condition and said cellular activity is TNF-induced cellular proliferation and/or anti-apoptotic characteristic.
23. The method according to claim 21 wherein said condition is an inflammatory condition and said cellular activity is the production of inflammatory mediators.
24. The method according to claim 23 wherein said inflammatory mediator is adhesion molecular expression.
25. The method according to claim 23 or 24 wherein said inflammatory condition is rheumatoid arthritis, atherosclerosis, asthma, autoimmune disease or inflammatory bowel disease.

- 62 -

26. The method according to any one of claims 20-25 wherein said agent is U0126.

27. The method according to any one of claims 20-25 wherein said agent is PD98059.

28. Use of an agent in the manufacture of a medicament for the treatment of a condition in a mammal, which condition is characterised by aberrant, unwanted or otherwise inappropriate cellular activity, wherein said agent modulates the phosphorylation of sphingosine kinase and wherein inducing or otherwise agonising said phosphorylation up-regulates said cellular activity and inhibiting or otherwise antagonising said phosphorylation down-regulates said cellular activity.

29. Use of an agent in the manufacture of a medicament for the treatment of a condition in a mammal, which condition is characterised by aberrant, unwanted or otherwise inappropriate sphingosine kinase activity, wherein said agent modulates the phosphorylation of sphingosine kinase and wherein inducing or otherwise agonising said phosphorylation up-regulates said sphingosine kinase activity and inhibiting or otherwise antagonising said phosphorylation down-regulates said sphingosine kinase activity.

30. Use according to claim 28 or 29 wherein said sphingosine kinase is human sphingosine kinase.

31. Use according to any one of claims 28-30 wherein said phosphorylation is modulated at S<sup>225</sup>.

32. Use according to claim 31 wherein said agent binds, links or otherwise associates with S<sup>225</sup>.

33. Use according to any one of claims 28-32 wherein modulation of said phosphorylation is modulation of proline-directed protein kinase catalysed phosphorylation.

- 63 -

34. Use according to claim 33 wherein said proline directed kinase is ERK1, ERK2 or CDK2.
35. Use according to claim 34 wherein said proline directed kinase is ERK2.
36. Use according to any one of claims 28-35 wherein said modulation is down-regulation.
37. Use according to claim 36 wherein said cellular activity is induced by TNF.
38. Use according to claim 37 wherein said condition is a neoplastic condition and said cellular activity is TNF-induced cellular proliferation and/or anti-apoptotic characteristic.
39. Use according to claim 37 wherein said condition is an inflammatory condition and said cellular activity is the production of inflammatory mediators.
40. Use according to claim 39 wherein said inflammatory mediator is adhesion molecular expression.
41. Use according to claim 39 or 40 wherein said inflammatory condition is rheumatoid arthritis, atherosclerosis, asthma, autoimmune disease or inflammatory bowel disease.
42. Use according to any one of claims 36-41 wherein said agent is U0126.
43. Use according to any one of claims 36-41 wherein said agent is PD98059.
44. A pharmaceutical composition comprising an agent, which agent modulates phosphorylation of sphingosine kinase, together with one or more pharmaceutically acceptable carriers and/or diluents when used in accordance with the method of any one of

- 64 -

claims 1-27.

45. An agent, which agent modulates phosphorylation of sphingosine kinase, when used in accordance with the method of any one of claims 1-27.

46. An isolated sphingosine kinase variant comprising a mutation in a region of said sphingosine kinase which region comprising a phosphorylation site, wherein said variant exhibits ablated or reduced phosphorylation capacity relative to wild-type sphingosine kinase or a functional derivative, homologue or analogue thereof.

47. An isolated sphingosine kinase variant comprising a mutation in a region of said sphingosine kinase which region comprising a phosphorylation site, wherein said variant exhibits enhanced or up-regulated phosphorylation capacity relative to wild-type sphingosine kinase or a functional derivative, homologue or analogue thereof.

48. The isolated variant of claim 46 wherein said variant comprises an amino acid sequence with a single or multiple amino acid substitution and/or deletion of amino acid S<sup>225</sup>.

49. The isolated variant of claim 48 wherein said substitution is a Ser<sup>225</sup> Ala substitution.